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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/580,523	ZHOU, XIAO-MAI	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-62 and 71-108* is/are pending in the application.

4a) Of the above claim(s) *31-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 1-30, 63-70 and adds new claims 71-108.

Accordingly, claims 71-108 are being examined.

The following are the remaining rejections.

REJECITON UNDER 35 USC 101, NEW REJECTION

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 71-108 are rejected under 35 USC 101 because the claims are directed to non-statutory subject matter.

The polypeptide as claimed has the same characteristics and utility as a polypeptide found naturally and therefore do not constitute patentable subject matter. In the absence of the hand of man, the naturally occurring polypeptide is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Amendment of the claims to recite " an isolated polypetide" is suggested to overcome this rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

1. Claims 71-76, 78-83, 85-93, 95-103, 105-108 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of "an amino acid conservative for alanine" claimed in Claims 71-76, 78-83, 85-93, 95-103, 105-108 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for replacement of Serine at amino acid position 118 of SEQ ID NO:1 with Alanine or amino acids other than serine (original claims 3, 16, p.41, lines 35-37). There is however no mention of amino acid conservative for alanine at the amino acid position 118 of SEQ ID NO:1.

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

2. If Applicant could overcome the above 112, first paragraph, Claims 99-108 are still rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of the specific sequence of amino acids 106-132 of SEQ ID NO:1 claimed in Claims 99, 103-108 has no clear support in the specification and the claims as originally filed.

The limitation of the specific sequence of amino acids 78-132 of SEQ ID NO:1 claimed in Claims 100-102 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for amino acids 106-131 of SEQ ID NO:1, corresponding to amino acids 143-168 of SEQ ID NO:2 (p.43, lines 5-8, and table 1 at page 41). There is however no mention of the specific sequence of amino acids 106-132, or 78-132 of SEQ ID NO:1.

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

Claims 71-108 are indefinite for the use of the language "position corresponding by sequence alignment to position 118 of SEQ ID NO:1" in claims 71, 75, 81, 82, 89, 92, 99, 102, because there is no reference point for alignment. Thus it is not clear which amino acid is referred to.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 71-108 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 71-108 are drawn to:

1) A polypeptide comprising an amino acid sequence at least 75%, 85%, 90% or 95% identical with SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine, and

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity (claims 71-74, 76-79).

2) The polypeptide of claim 74, wherein said polypeptide comprises SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 75).

3) A polypeptide comprising an amino acid sequence at least 75% identical with amino acids 114 to 122 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 10 or 25 amino acids long (clailms 81, 83-88).

4) The polypeptide of claim 81, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 114-122 of SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 82).

5) A polypeptide comprising an amino acid sequence at least 75%, 85% or 90% identical with amino acids 103-123 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 25 amino acids long (claim 89-91, 93-98).

6) The polypeptide of claim 91, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 103-123 of SEQ ID NO:1, except that the

amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 92).

7) A polypeptide comprising an amino acid sequence at least 75% identical with amino acids 103-123, or at least 85% or 90% identical to amino acids 78-132 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 25 amino acids long (claims 99-101, 103-108).

8) The polypeptide of claim 101, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 78-132 of SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 102).

The specification discloses that BAD, a cell death promoter, is shown to share identity with Bcl-2 only within the BH3 domain (p. 3, last paragraph), and that the BH3 domain, consisting of amino acids 114-122 of the human BAD of SEQ ID NO:1 (p. 13, lines 15-16), is necessary for forming heterodimers with Bcl-X_L or Bcl-2 (p.2, last

paragraph, bridging p.3) . It is noted that the wild type BH3 domain contains the amino acid Serine 118.

The specification further discloses that BAD, when dephosphorylated, binds to and form a heterodimer with Bcl-X_L, resulting in promoting cell death by another cell death promoter, BAX (p.4, first paragraph). In a post filing date, Letai, A et al, 2002, Cancer Cell, 2: 183-192, teach that the peptide consisting of BAD BH3 domain by itself could occupy the pocket of anti-apoptic Bcl-2, and displaces the BID-like domain from binding to Bcl-2; said free BID-like domain now could bind to and activate pro-apoptotic BAX or BAK, resulting in apoptosis (abstract).

The specification also discloses that phosphorylation at Serine 155 of murine BAD SEQ ID NO:2 (which corresponds to Serine 118 of human BAD of SEQ ID NO:1) directly abolishes the affinity of its BH3 domain for Bcl-X_L (p.92, last paragraph), and that human BAD, similar to murine BAD SEQ ID NO:2, when phosphorylated at serine 118, is unable to bind to and inhibit the survival promoter, Bcl-X_L, resulting in promoting cell survival (p.7, paragraph under Summary).

The specification discloses that mutation of Serine 155 of murine BAD SEQ ID NO:2 to Alanine, a nonphosphorylatable residue, results in increased cell death. The specification discloses that when Ser155 is replaced with Aspartic acid (S155D), to mimic the negatively charged phosphorylated Ser 155 residue, no pro-apoptotic activity as compared to the wild-type BAD is found, indicating that phosphorylation of Ser 155 leads to inactivation of BAD in cells (Example 8, pages 86-87, p.89, second paragraph).

A. Because one cannot determine which amino acid is the reference point for sequence alignment, **the claims 71-108 encompass variants of SEQ ID NO:1, wherein said variant could have substitution with alanine at any amino acids** throughout the whole length of the polypeptide of SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1, in addition to addition, deletion or substitution at any amino acid within SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1, because the claimed variants only need to be 75%, 85%, 90% or 95% similar to SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1.

One cannot predict whether the claimed polypeptide still have the function of promoting cell death, or binding to Bcl-X_L or Bcl-2, in view that It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, and that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible

in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), of record, who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252), of record. Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54, all of record). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, it is clear that there is no correlation between the cited structure of the claimed variant BAD polypeptide, wherein any amino

acid position of SEQ ID NO:1 could be substituted with alanine, and the function of cell death promoting activity, or binding to Bcl-X_L, or Bcl-2.

B. Further, even if the only alanine substitution is at position 118 of SEQ ID NO:1, **claims 71-74, 76-80 encompass a variant BAD sequence that does not necessarily have the whole BH3 domain (amino acids 114-122 of SEQ ID NO:1), except the presence of a single amino acid SER118A, or a variant BAD sequence that contains the variant BH3 domain, in which, except for SER118A, any other amino acids in the BH3 domain could have any deletion, addition, or substitution with any amino acids**.

It is noted BH3 domain is necessary for the binding of BAD to Bcl-X_L, or Bcl-2, a step necessary for inducing apoptosis action by a free BAX (specification, p.2, last paragraph, bridging p.3, and Letai et al, 2002, surpra). Further, it is known in the art that a mutated BH3 domain, such as the BH3 domain of BID, with two substitutions at L90A and D95A, loss the ability to cause cytochrome c release, and thus subsequent apoptosis (Letai, A et al, supra, p.184, second column, last four line of the first paragraph under Results).

Therefore, in view of the above teaching, one cannot predict that the claimed variant BAD polypeptide, missing the entire BH3 domain, or having a variant BH3 domain, wherein except for SER118A, any other amino acids in said variant BH3 domain could have any deletion, addition, or substitution with any amino acids, could promote cell death, or bind to Bcl-X_L, or Bcl-2, or having sufficient binding affinity to displace and free BAX from Bcl-X_L, or Bcl-2.

In view of the above unpredictability, it is clear that there is no correlation provided between the properties of "cell death promoting activity, Bcl-X_L binding activity, or Bcl-2 binding activity" and structure of "a polypeptide comprising an amino acid sequence that has at least 75% sequence identity with SEQ ID NO:1, wherein the amino acid position 118 of SEQ ID NO:1 is alanine".

The recitation of a single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variant of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, is not an adequate description of the claimed genus of variant BAD polypeptides that could promote cell death, or bind to Bcl-X_L or Bcl-2, because there is no correlation between the recited structure and the function of promoting cell death or binding to Bcl-X_L or Bcl-2, and because the recited single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, is not a representative number of species.

C. In addition, even if the only alanine substitution is at position 118 of SEQ ID NO:1, **claims 81, 83-84, 86-91, 93-94, 96-101, 103-104, 106-108 encompass a sequence comprising variant BH3 domain, wherein except for SER118A, any other amino acids in the BH3 domain could have any deletion, addition or substitution with any amino acids**.

Except for a single polypeptide of SEQ ID NO:1 containing S118A, the specification does not describe any polypeptide variants of SEQ ID NO:1 containing S118A and a variant BH3 domain, wherein except for SER118A, any other amino acids in the BH3 domain could have any deletion, addition or substitution with any amino acids.

Further, the specification does not describe which amino acids of the BH3 domain, other than substitution of Ser118 with alanine, could be deleted, added and substituted with any amino acids, such that the claimed polypeptide comprising such variant BH3 domain still could promote cell death activity, or bind to Bcl-X_L, or Bcl-2.

In view of the teaching of Bowie, Burgess et al, Lazar et al, Tao et al, Gillies et al, and Letai et al, supra, one cannot predict that the claimed polypeptides comprising the variant BH3 domain, wherein except for SER118A, any other amino acids in the BH3 domain could have any deletion, addition or substitution with any amino acids, still could promote cell death or bind to Bcl-X_L, or Bcl-2.

Thus, it is clear that there is no correlation provided between the properties of "cell death promoting activity, Bcl-X_L binding activity, or Bcl-2 binding activity" and structure of "a polypeptide comprising an amino acid sequence that has at least 75% sequence identity with SEQ amino acids 114-122, 103-123, 106-132, 78-132 of ID NO:1, wherein the amino acid position 118 of SEQ ID NO:1 is alanine".

The recited single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of

SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, are not a representative number of species.

D. Further, **claims 78-79, 85-86, 95-96, 105-106 encompass a variant BAD polypeptide wherein the amino acid position 118 could be any amino acids other than alanine or glycine.**

One cannot predict that a variant BAD polypeptide wherein the amino acid position 118 could be any amino acid, other than alanine or glycine could promote cell death, in view of the teaching in the specification that when SER155 of the murine BAD of SEQ ID NO:2 (which is equivalent to SER118 of the human BAD of SEQ ID NO:1) is replaced with aspartic acid (S155D) to mimic the negatively charged phosphoserine 155 residue, no pro-apoptotic activity is found (specification, p.89, second paragraph).

Further, one cannot predict whether the claimed variant BAD, wherein the amino acid position 118 could be any amino acids, other than alanine or glycine, has sufficient affinity for Bcl-X_L or Bcl-2, in view that the BAD BH3 domain has to fit into the pocket of anti-apoptotic Bcl-2, and displaces the BID-like domain from binding to Bcl-2, as taught by Letai et al, supra, and that one cannot predict whether any amino acids at position 118 of SEQ ID NO:1 would not change the conformation of the BAD BH3 domain.

The specification does not describe any BAD variant polypeptides, wherein the amino acid position 118 could be any amino acid, other than alanine or glycine, and wherein such polypeptide still could promote cell death, or bind to Bcl-X_L or Bcl-2.

In view of the above, it is clear that there is no correlation between the recited structure in claims 78-79, 85-86, 95-96, 105-106 and the function of promoting cell death or binding to Bcl-X_L or Bcl-2.

Further, the recited single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, are not a representative number of species.

E. In addition, it is noted that **the function of binding to Bcl-X_L or Bcl-2 is not a definitive function that defines the claimed BAD polypeptide, and does not correlate with the structure of a BH3 domain**, because there are other polypeptides with completely different structure that bind to Bcl-X_L or Bcl-2, via a different domain, such as BAX which binds to Bcl-2 via its BH1 or BH2 domain (Yin XM et al, 1994, Nature, 369: 321-323), which does not exist in BAD.

Although the specification discloses a single variant of the human BAD polypeptide of SEQ ID NO:1, wherein Serine 118 is replaced with Alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, this does not provide a description of the claimed genus of variant BAD polypeptides.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University

of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that A [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials.Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling

within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the claimed variant BAD polypeptide, by structurally describing a representative number of variant BAD polypeptides, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, as shown in the example of Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe variant BAD polypeptide in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide the complete structure of any variant BAD polypeptide other than a single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine, this does not provide a description of the claimed variant BAD polypeptides, that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe the claimed variant BAD polypeptides, by the standards in the example in Lilly. The specification describes only a single variant human BAD polypeptide of SEQ ID NO:1, wherein amino acid position 118 is alanine, and two variants of murine BAD polypeptides of SEQ ID NO:2 and 3, wherein the equivalent Serine at position 155 and 113, respectively, is replaced with Alanine. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

One of skill in the art would conclude that Applicant did not have possession of a genus of variant BAD polypeptides at the time the invention was made.

Thus, the specification does not provide an adequate written description of the claimed variant BAD polypeptides, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 71-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:1, wherein its amino acid at position 118 is Alanine, and wherein said polypeptide has in vitro cell death promoting activity, does not reasonably provide enablement for :1) A polypeptide comprising an amino acid sequence at least 75%, 85%, 90% or 95% identical with SEQ ID NO:1, wherein a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine, and b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, or 2) A polypeptide comprising an amino acid sequence at least 75%, 85%, 90% identical with amino acids 114 to 122, or 103-123, 106-132, or 78-132 of SEQ ID NO:1, wherein a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine, b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 71-108 are drawn to:

1) A polypeptide comprising an amino acid sequence at least 75%, 85%, 90% or 95% identical with SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine, and

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity (claims 71-74, 76-79).

2) The polypeptide of claim 74, wherein said polypeptide comprises SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 75).

3) A polypeptide comprising an amino acid sequence at least 75% identical with amino acids 114 to 122 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 10 or 25 amino acids long (claims 81, 83-88).

4) The polypeptide of claim 81, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 114-122 of SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 82).

5) A polypeptide comprising an amino acid sequence at least 75%, 85% or 90% identical with amino acids 103-123 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 25 amino acids long (claim 89-91, 93-98).

6) The polypeptide of claim 91, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 103-123 of SEQ ID NO:1, except that the

amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 92).

7) A polypeptide comprising an amino acid sequence at least 75% identical with amino acids 103-123, or at least 85% or 90% identical to amino acids 78-132 of SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine,

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity, and

c) said polypeptide could be at least 25 amino acids long (claims 99-101, 103-108).

8) The polypeptide of claim 101, wherein said polypeptide comprises an amino acid sequence that is identical to amino acids 78-132 of SEQ ID NO:1, except that the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is alanine or an amino acid conservative for alanine (claim 102).

The claims 71-108 encompass variants of SEQ ID NO:1, wherein said variant could have substitution with alanine at any amino acids throughout the whole length of the polypeptide of SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1, in addition to addition and deletion at any amino acids within SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1, because the

claimed variants only need to be 75%, 85%, 90% or 95% similar to SEQ ID NO:1, or amino acids 114-122, 103-123, 106-132, 78-132 of SEQ ID NO:1.

In addition, claims 71-74, 76-80 also encompass variants of SEQ ID NO:1, wherein said variants do not necessarily have the full length BH3 domain, except the presence of SER118A, or variants of SEQ ID NO:1 that contain the variant BH3 domain, wherein except for SER118A, the other amino acids in the BH3 domain could have any deletion, addition, or substitution with any amino acids.

Claims 81, 83-84, 86-91, 93-94, 96-101, 103-104, 106-108 encompass a sequence that comprises variant BH3 domain, wherein except for SER118A, any other amino acids in the BH3 domain could have any deletion, addition or substitution with any amino acids.

Further, claims 78-79, 85-86, 95-96, 105-106 encompass a variant BAD polypeptide wherein the amino acid position 118 could be any amino acids, other than alanine or glycine.

One cannot predict whether the claimed polypeptide still have the function of promoting cell death, or binding to Bcl-X_L or Bcl-2, in view that it is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, and that protein chemistry is probably one of the most unpredictable areas of biotechnology, as taught by Bowie, Burgess et al, Lazar et al, Tao et al, and Gillies et al, supra.

Further, it is noted BH3 domain is necessary for the binding of BAD to Bcl-X_L, or Bcl-2, a step necessary for inducing apoptosis action by a free BAX (specification, p.2, last paragraph, bridging p.3, and Letai et al, 2002, surpra). In addition, it is known in the art that a mutated BH3 domain, such as the BH3 domain of BID, with two substitutions at L90A and D95A, loss the ability to cause cytochrome c release, and thus subsequent apoptosis (Letai, A et al, supra, p.184, second column, last four line of the first paragraph under Results).

Therefore, in view of the above teaching, one cannot predict that the claimed variant BAD polypeptide, missing the entire BH3 domain, or having a variant BH3 domain, wherein except for SER118A, any other amino acids in said variant BH3 domain could have any deletion, addition, or substitution with any amino acids, could promote cell death or bind to Bcl-X_L, or Bcl-2, or have sufficient binding affinity to displace and free BAX from Bcl-X_L, or Bcl-2.

Further, one cannot predict that a variant BAD polypeptide wherein the amino acid position 118 could be any amino acid, other than alanine or glycine could promote cell death, in view of the teaching in the specification that when SER155 of the murine BAD of SEQ ID NO:2 (which is equivalent to SER118 of the human BAD of SEQ ID NO:1) is replaced with aspartic acid (S155D) to mimic the negatively charged phosphoserine 155 residue, no pro-apoptotic activity is found (specification, p.89, second paragraph).

Further, one cannot predict whether the claimed variant BAD, wherein the amino acid position 118 could be any amino acid, other than alanine or glycine has sufficient

affinity for Bcl-X_L or Bcl-2, in view that the BAD BH3 domain has to fit into the pocket of anti-apoptotic Bcl-2, and displaces the BID-like domain from binding to Bcl-2, as taught by Letai et al, supra, and that one cannot predict whether any amino acids at position 118 of SEQ ID NO:1 would not change the conformation of the BAD BH3 domain, in view of the teaching of Bowie, supra.

The specification does not disclose how to make the claimed variant BAD polypeptides, such that they would function or have the properties as claimed, or how to use said variant BAD polypeptides, if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

New claims 71-108 are rejected under 35 USC 102(e) as being anticipated by US 5,965,703, for reasons already of record in paper of 02/10/05.

Applicant argues that the new claims recite polypeptides wherein the amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1 is alanine or an amino acid conservative for alanine. Applicant argues that the rejection is obviated, because SEQ ID NO:2 of the '703 patent includes a serine at position 118.

Applicant argues that "the amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1" is clearly defined in the specification. Applicant argues that the specification on pages 9, 41, 45 describes how sequence

alignment allows identification of regions of sequence homology, i.e. the sequence alignment allows identification of the serine or other amino acid at a position corresponding to the serine at a position 118 of SEQ ID NO:1. Applicant argues that similarly, page 50 of the specification and table 1 at page 41 indicate that the position corresponding to Ser 118 of SEQ ID NO:1 can be identified by alignment of the sequence of a mutant BAD or fragment thereof with SEQ ID NO:1.

Applicant further argues that numerous references, such as Tatusova et al, Altschul et al, describe the use of sequence alignment to compare related polypeptide sequences.

The recitation of Tatusova et al, Altschul et al is acknowledged and entered.

Applicant's arguments set forth in paper of 07/07/05 have been considered but are not deemed to be persuasive for the following reasons:

The specification only describes the results of the alignment, i.e. the position corresponding to position 118 of SEQ ID NO:1 is determined by alignment of mutant BAD with SEQ ID NO:1 (p.9), the alignment "allows" identification of regions of sequence homology, such as the BH3 domain, or the serine at position of 118 of SEQ ID NO:1 (p.45), and the actual alignment of different sequences in table 1 on page 41.

Thus the term "the amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1" is not defined by the specification, nor it is limiting.

Because one cannot determine which amino acid is the reference point for sequence alignment in the claims, any amino acid could correspond by sequence alignment to position 118 of SEQ ID NO:1.

Further, even the corresponding amino acid is serine 118 of the art BAD polypeptide, claims 78, 85, 95, 105 encompass a variant BAD polypeptide, wherein the amino acid position 118 could be any amino acids other than alanine, e.g. serine, and thus clearly is the same as the art polypeptide.

Thus claimed polypeptides seem to be the same as the prior art BAD polypeptide, which is 100% similar to SEQ ID NO:1 of the claimed invention, and which promotes cell death, and binds to human Bcl-X_L, and Bcl-2.

Although the reference does not specifically teach a polypeptide, wherein the amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1 is alanine or an amino acid conservative for alanine, or is not alanine, or is not glycine, however, the claimed polypeptides appear to be the same as the prior art polypeptide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

REJECTION UNDER 35 USC 102(e), NEW REJECTION

Claims 78-79 are rejected under 35 USC 102(e) as being anticipated by US 5,965,703, of record, for the same reasons already of record in paper of 12/19/01.

New claims 78-79 are drawn to:

A polypeptide comprising an amino acid sequence at least 75% identical with SEQ ID NO:1, wherein

a) the amino acid at the position corresponding by sequence alignment to position 118 or SEQ ID NO:1 is not alanine, or is not glycine, and

b) said polypeptide has at least one in vitro activity selected from the group consisting of cell death promoting activity, Bcl-X_L binding activity, and Bcl-2 binding activity.

US 5,965,703 teaches a mouse BAD sequence which is 75% similar to the claimed SEQ ID NO:1, from amino acid 1 to 168, i.e. the entire length of the claimed SEQ ID NO: 1, wherein the amino acid at the position corresponding the amino acid position 118 of SEQ ID NO:1, **by sequence alignment**, is threonine, under sequence similarity search (MPSRCH search report, 09-580523-1b-rai, pages 4-5, SEQ ID NO:3, of record).

US 5,965,703 further teaches that the recited sequence of SEQ ID NO:3 is mouse Bcl-X_L and/or Bcl-2 associated death (BAD) promoting polypeptide (figure 2 legend on column 3),wherein the mouse BAD shares the highest degree of homology with other Bcl-2 related proteins in the region believed to contain the binding site with Bcl-X_L and Bc1-2 (column 6, second paragraph), and wherein members of the Bcl-2

family are able to bind Bcl-X_L and Bcl-2 (column 3, paragraph under detailed description of the invention).

Given the polypeptide sequence taught by US 5,965,703, one of ordinary skill in the art would immediately envision the claimed polypeptide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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MINH TAM DAVIS

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